Recent developments and advances in atopic dermatitis and food allergy

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Abstract: This review highlights recent advances in atopic dermatitis (AD) and food allergy (FA), particularly on molecular mechanisms and disease endotypes, recent developments in global strategies for the management of patients, pipeline for future treatments, primary and secondary prevention and psychosocial aspects. During the recent years, there has been major advances in personalized/precision medicine linked to better understanding of disease pathophysiology and precision treatment options of AD. A greater understanding of the molecular and cellular mechanisms of AD through substantial progress in epidemiology, genetics, skin immunology and psychological aspects resulted in advancements in the precision management of AD. However, the implementation of precision medicine in the management of AD still requires the validation of reliable biomarkers, which will provide more tailored management, starting from prevention strategies towards targeted therapies for more severe diseases. Cutaneous exposure to food via defective barriers is an important route of sensitization to food allergens. Studies on the role of the skin barrier genes demonstrated their association with the development of IgE-mediated FA, and suggest novel prevention and treatment strategies for type 2 diseases in general because of their link to barrier defects not only in AD and FA, but also in asthma, chronic rhinosinusitis, allergic rhinitis and inflammatory bowel disease. The development of more accurate diagnostic tools, biomarkers for early prediction, and innovative solutions require a better understanding of molecular mechanisms and the pathophysiology of FA. Based on these developments, this review provides an overview of novel developments and advances in AD and FA, which are reported particularly during the last two years.

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Invited Review Article

Recent developments and advances in atopic dermatitis and food allergy

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ABSTRACT

This review highlights recent advances in atopic dermatitis (AD) and food allergy (FA), particularly on molecular mechanisms and disease endotypes, recent developments in global strategies for the management of patients, pipeline for future treatments, primary and secondary prevention and psychosocial aspects. During the recent years, there has been major advances in personalized/precision medicine linked to better understanding of disease pathophysiology and precision treatment options of AD. A greater understanding of the molecular and cellular mechanisms of AD through substantial progress in epidemiology, genetics, skin immunology and psychological aspects resulted in advancements in the precision management of AD. However, the implementation of precision medicine in the management of AD still requires the validation of reliable biomarkers, which will provide more tailored management, starting from prevention strategies towards targeted therapies for more severe diseases. Cutaneous exposure to food via defective barriers is an important route of sensitization to food allergens. Studies on the role of the skin barrier genes demonstrated their association with the development of IgE-mediated FA, and suggest novel prevention and treatment strategies for type 2 diseases in general because of their link to barrier defects not only in AD and FA, but also in asthma, chronic rhinosinusitis, allergic rhinitis and inflammatory bowel disease. The development of more accurate diagnostic tools, biomarkers for early prediction, and innovative solutions require a better understanding of molecular mechanisms and the pathophysiology of FA. Based on these developments, this review provides an overview of novel developments and advances in AD and FA, which are reported particularly during the last two years.

Introduction

There are remarkable recent developments understanding the mechanisms, diagnostic and therapeutic management of atopic dermatitis (AD) and food allergy (FA) and differences in the practice by dermatologists and pediatricians in different countries. AD is a chronic inflammatory pruritic skin disease that affects a large number of children and adults in industrialized countries. Its worldwide prevalence, ranges from 0.2% to 24.6%, with the highest prevalence of AD in childhood in Africa and Latin America.[1] The onset of AD occurs during the first year of life in 60% of the children.[2] The prevalence of AD in the first 2 years of life is 21.5%.[3] 43.2% of these children have spontaneous outgrow of the disease, 38.3% persist with mild AD and mild rhinitis and 18.7% persist with severe disease and show an extensive atopic march including FA, asthma, and rhinitis.[3] Only 16.8% of AD patients have onset after adolescence.[4] AD and FA are extensively overlapping. The prevalence of FA has been suggested to increase in the last two decades and is in the range of 4% in food challenge tests in 1 year, which increases to 6–8% in questionnaire surveys.[5] FA shows various different clinical presentations with respect to responsible allergens, age at presentation, timing of reaction, presence of comorbid atopic diseases, outgrow and resolution with time, and response to immunotherapy. This heterogeneity of clinical presentations of FA possess a challenge to successful management and treatment. Avoidance of allergenic foods and the use of epinephrine in case of a severe reaction triggered by accidental ingestion remain the standard of care, as there are currently no approved treatments for FA. Dysregulated immune response patterns and their heterogenous and complex combination in chronic inflammation, immune cell and tissue cell hyperresponsiveness, microinflammation even at the

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healing stage and tissue remodeling in affected tissues define the complexity of FA and AD.

Modern healthcare is rapidly developing and staying away from the concept of including all of the patients in one basket to an individualized response with the combination of precision diagnosis and personalized treatment. An overarching medicinal concept is developing with better understanding of genotypes, phenotypes, endotypes, regiotypes, biomarkers and theratypes of diseases that also fully include AD and FA.[6] More than 100 years old allergen-specific management of allergic diseases has particularly contributed to the early awareness in precision medicine. Multipleomics, big data, and systems biology have demonstrated a profound complexity and dynamic variability in AD and FA between individuals, as well as between regions.[6]

Basic research has intensified during the recent years to better understand the immune and inflammatory mechanisms in AD and FA. IgE sensitization, essential molecular pathways of type 2 response, mechanisms of disease outgrow and therapy response are important in both diseases. Mechanisms of desensitization, successful ways of treatment without side effects and short- and long-term tolerance mechanisms are key research areas in FA. This article highlights and summarizes key advances in AD and FA published during the last couple of years. Important ones from these achievements are summarized in Tables 1 and 2.

Global strategies for the assessment and management of atopic dermatitis

There is a consistent association of AD with other atopic diseases including asthma and FA. The concept of atopic march was developed to describe the progression of these atopic diseases in children.[7] Although it most often starts in infancy, it is also highly prevalent in adults.[8] Among the adult AD population, a multidimensional burden has been described not only including dermatologic symptoms, but also increased socioeconomic burden, sleep disorders, and reductions in health-related quality of life and work productivity.[9–11] With increasing severity, the multidimensional burdens listed above also increase. International Classification of Diseases, 11th Revision (ICD-11) was provided,[12] and ICD-9, clinical modification codes alone were found to be insufficient for identification of AD from healthcare databases, but incorporation of the diagnosis of asthma, hay fever, and FA improved the positive predictive value and specificity of these searches.[13] The Harmonizing Outcomes Measures for Eczema (HOME) initiative is an evidence driven and evidence-generating outcomes research initiative that aims to develop standardization of a core set of outcome measurements of atopic eczema, which is also known as AD or eczema.[14,15] Various instruments exist to measure symptoms in AD to assess safety and efficacy of therapies in clinical trials.[16,17] Among 18 instruments, the pediatric Itch Severity Scale (ISS), Patient-Oriented Eczema Measure (POEM), Patient-Oriented SCOring Atopic Dermatitis (PO-SCORAD), Self-Administered Eczema Area and Severity Index (SA-EASI), and adapted SA-EASI are currently recommended for assessing symptoms of AD in future clinical trials.[18] However, the use of simple patient-reported global AD severity scores is feasible for clinical practice and epidemiological research. A simple scoring system of mild, moderate, and severe patient-reported AD severity correlated well with objective AD assessments, objective SCORAD, and EASI.[19] Patient-reported AD severity may be sufficiently valid for assessing AD severity. For the management of AD, patient's increased adherence to topical medication is indispensable particularly with use of topical corticosteroids. The topical corticosteroid phobia (TOPICOP) score is available for the assessment of topical corticosteroid phobia based on 12 items.[20] TOPICOP scorings can feasibly be applied internationally and can be used to obtain data from studies and to adapt patient education and treatment.[21]

The lifetime prevalence of atopic diseases is significantly increasing from adolescence to adulthood, particularly that of allergic rhinitis.[22] Regarding the clinical course of AD, no significant difference in AD prevalence before and after childhood has been found by systemic review and meta-analysis of longitudinal

Table 1
Key developments and advances in atopic dermatitis (AD).

Developments and Advances	References
Global strategies for the assessment and management of AD	
Validation of International Classification of Disease	Hsu *et al.*[13]
Evaluation of symptom measurement instruments	Blauvelt *et al.*[17], Vakharia *et al.*[19], Stalder *et al.*[21]
Lifetime prevalence	Mortz *et al.*[22], Abuabara *et al.*[23], Barbarot *et al.*[24]
Product-specific standardization	Zimmer *et al.*[26], Bonertz *et al.*[28]
Prevention of AD	
Atopic march	Han *et al.*[29], Ferreira *et al.*[31]
Microbiome and immune system	Chu *et al.*[35]
Prevention approach to decrease AD	Elbert *et al.*[38], Roduit *et al.*[41], Silverwood *et al.*[43]
Psychological aspects of AD	
Management of psychological status	Ronnstad *et al.*[48]
Attention-deficit/hyperactivity disorder	Schmitt *et al.*[53]
Mechanisms and pathophysiology of AD	
microRNA and AD	Carreras-Badosa *et al.*[60]
Periostin and epidermal barrier	Mitamura *et al.*[61], Izuhara *et al.*[62]
Biomarker	Czarnowicki *et al.*[65]
T-cell receptor repertoire	Brunner *et al.*[66]
Mast cells and sphingosine-1-phosphate activation	Wedman *et al.*[69]
Langerhans and inflammatory dendritic epidermal cells	Otsuka *et al.*[72]
Aryl hydrocarbon receptor mediated anti-inflammatory feed back	Koch *et al.*[75]
Therapeutic targets and experimental models for the treatment of AD	
Allergen specific immunotherapy	Shin *et al.*[131]
Oral tolerance	Baek *et al.*[77]
Topical ivermectin	Ventre *et al.*[79]
Mesenchymal stem cells	Song *et al.*[80]
Antimicrobial peptide	Kopfnagel *et al.*[83]
Chemokine receptors	Murray *et al.*[85]
BCG vaccination	Thostesen *et al.*[87]

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Table 2
Key developments and advances in food allergy (FA).

Developments and Advances	References
Diagnosis and the role of biomarkers in early prediction	
Precision medicine in FA	Agache *et al.*[6], Flores *et al.*[97]
Assessing basophil activation	Mukai *et al.*[95]
Prediction of FA	Datema *et al.*[100], Pettersson *et al.*[109], Baumert *et al.*[111]
Predictive biomarkers of anaphylaxis	Turner *et al.*[112]
Innovative solutions	
Allergen exposure chambers	Rosner-Friese *et al.*[124], Pfaar *et al.*[126]
Companion animal research	Jensen-Jarolim *et al.*[134]
Mechanisms and pathophysiology	
Vitamin D and mast cell stabilization	Liu *et al.*[145]
Epigenetic mechanisms	Asai *et al.*[150]
Intestinal microbiome and food sensitization	Savage *et al.*[149]
microRNA and FA	D'Argenio *et al.*[153]
Tolerance development	Sampson *et al.*[147]
Characterization of the T-cell response	Zulehner *et al.*[164]
Novel strategies for the treatment and management	
Allergen immunotherapy	Burks *et al.*[166], Wood[171], Ryan *et al.*[174]
Patient's quality of life	Rigbi *et al.*[168]
Nanoparticles for allergen-specific immunotherapy	Pohlit *et al.*[176]
Combination therapy	MacGinnitie *et al.*[173]
Early peanut and egg introduction	Greenhawt *et al.*[180], Shaker *et al.*[182]

studies.[23] In studies of AD prevalence by country, estimations of adult AD prevalence ranges from 2.1% to 4.9%.[24] For international clinical and epidemiological research, it is becoming increasingly clear that differing nomenclature of the disease has important harmful or unwanted consequences.[25] AD as well as the term atopic eczema describe clinically chronic relapsing pruritic inflammatory skin conditions. In this context, the International Eczema Council (IEC) noted that the term eczema is imprecise and confusing and recommended the use of AD or atopic eczema in all publications, presentations and discussions about the disorder.[25]

Product-specific standardization is of critical importance for patients with suspected or proven allergy.[26] Ensuring persistent quality, safety, and efficacy of medical allergen products is required for an effective treatment. Products for allergen immunotherapy (AIT) have been approved by national authorities; however, different regulations exist worldwide. Although regulatory framework in the European Union (EU) has been developed in the field of AIT, it remains heterogeneous. New allergen products for AIT are being developed and manufactured each year. However, despite the increased number of medical products such as AIT, regulatory framework for quality parameters has not yet been reached. Thus, it is extremely complicated and challenging to develop a harmonized international approach to regulation. International pharmaceutical companies have recently placed an emphasis on medical products that promote health and supply local and neighboring markets as well as global markets. Therefore, it is quite important to understand the regulation of allergen products from a global perspective. From these kind of circumstances, the EAACI Taskforce on Regulatory Aspects of Allergen Immunotherapy, as a part of the EAACI AIT Guidelines, analyzed how products for the diagnosis of allergies and AIT are regulated in different countries and regions worldwide.[27] They also provided an overview of how AIT products are regulated with respect to their manufacturing and quality in EU, and United States.[28] They described similarities and differences in the regulation of allergen manufacturing and quality control between the EU and United States.

Prevention of atopic dermatitis

The development of AD in infancy and subsequent conditions such as FA, asthma, and allergic rhinitis has been observed as co-manifestation or occurring in sequence. These longitudinal associations have been known to lead to atopic march,[29] and an association between AD and birch pollen allergy has also been reported.[30] There has been controversy regarding whether atopic march is the primary causal factor in childhood allergic diseases. A recent study indicated that AD, asthma and allergic rhinitis partly coexist, because they share many genetic risk variants that dysregulate the expression of immune-related genes.[31] Another study showed that the risk of developing asthma or allergic rhinitis was much higher in IgE-associated AD compared to nonallergic AD.[32] Therefore, it has been argued that it is important to distinguish between eczema with and without IgE sensitization when considering the implications of allergic diseases in infancy.[32,33]

Environmental factors, such as bacteria influence the human microbiome and immune system. Development of novel preventative approaches is important, and a recent review summarizes current evidence for the potential of bacteria and their metabolites in the prevention of allergic diseases.[34] Early life microbial exposure influences the risk of allergies and development of a balanced immune system.[35,36] Not only the exposure, but also the correct composition of the gut microbiota have a role in allergy development.[37]

Furthermore, the increased incidence of AD and the progression from AD to allergic rhinitis and asthma have highlighted the need for disease prevention. A recent article indicates that shorter duration or non-exclusive breastfeeding was associated with a weak overall increased risk of AD, but not sensitization.[38] Concerning the influence of pregnancy-related and perinatal factors, children who are born by cesarean section and assisted-delivery showed significant associations with AD, asthma and atopic sensitization in childhood.[39] Effect of food diversity in childhood has also been investigated. The consumption of cheese had a significant protective effect for AD.[40] The effect on AD may be associated with the diversity of consumed cheese, including those rich in microbial diversity. It has to be noted here that cheese is an important provider of short chain fatty acids that are linked to prevention of AD in children and mouse models.[41] Despite a preventative approach to decrease AD in early-childhood, some patients may have persistent disease into adulthood. However, the prevalence of comorbidities in patients with AD is not well characterized.[42] Recent studies have shown that patients with severe AD had a high prevalence of smoking, stroke, cardiovascular disease, inflammatory bowel disease, depression and anxiety.[42,43]

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These comorbidities might represent targets for prevention and intervention of AD management.

Psychological aspects of atopic dermatitis

AD has been thought to carry an increased risk for mental disorders.[8] However, few studies have reported the prevalence of psychiatric disorders among adults with AD. A recent study revealed that adolescents with AD from Korea are associated with a higher prevalence of depression symptoms and suicidal behaviors.[44] A poor health-related quality of life is linked with depressive mood, depression, and suicidal ideation, which are, in turn, associated with AD.[45] Therefore, improving poor health-related quality of life and managing psychological status in AD among adolescents are critical. From a population-based survey using large-scale observational data, association among depression, anxiety, and AD has been analyzed.[46] The risk of hospitalization and suicide was also examined. They found a significant association between self-reported AD among adults and clinician-diagnosed psychiatric status, including depression and anxiety.[46] Moreover, a recent study of the association between AD and suicidality suggests that patients with AD are at an increased risk of suicidal ideation and suicide attempts.[47] However, depression, anxiety, and suicidal ideation do not lead to psychiatric consultations, hospitalization, or suicide.[46] One study reported that improvement of AD appears to be reduced these psychiatric conditions.[48]

Epidemiological studies using standardized diagnostic criteria suggest that 3%–6% of the child population may suffer from attention-deficit/hyperactivity disorder (ADHD) and more recently, a relevant association between AD and ADHD has been reported.[49,50] Moreover, children with ADHD are more likely to have not only AD but asthma, allergic rhinitis, and allergic conjunctivitis than their counterparts.[51] A Swedish birth cohort study found that preschool eczema was not associated with ADHD medication at school age.[52] To shed more light on the comorbidity of AD and ADHD, Schmitt *et al.* hypothesized that children with AD, who do not meet the complete diagnostic criteria of AD frequently show features of ADHD and increased mental health problems.[53] They concluded that even if the clinical diagnosis of ADHD is excluded, children with AD show increased levels of ADHD symptoms.[53] Despite these findings, the underlying biological mechanisms still require further investigation. Therefore, prevention and effective treatment of AD represent unmet needs in children as well.

Mechanisms and pathophysiology of atopic dermatitis

Major mechanisms of AD include abnormalities in the terminal differentiation of keratinocytes that lead to a defective stratum corneum.[54,55] A defective barrier in AD allows the penetration of allergens and microbes, leading to IgE sensitization and type 2 cytokine production that drives allergic inflammation.[56] At least two AD subtypes can be distinguished: the first type is characterized by a strong type 2 mediated response with high levels of serum immunoglobulin E (IgE) and the second is a nonallergic type characterized with normal IgE levels.[8,57] MicroRNAs (miRNAs) are short, single-stranded RNA molecules that regulate Th2 skewing and influence innate and adaptive immune responses.[58,59] Among miRNAs, miRNA-146a is needed for the production of IgE and linked to the modulation of Th1/Th17 cell mediated responses in mice.[60] A matricellular protein, periostin, is induced by Th2 cytokines IL-4 or IL-13 and plays an important role in barrier dysfunction. A recent study shows that IL-24, produced in keratinocytes downstream of periostin and IL-13, decrease filaggrin expression that leads to barrier dysfunction in AD.[61,62] In AD, Th2 cells as well as other T-cell subpopulations (Th1, Th17, and Th22) are detectable in the AD skin lesions. Figure 1 shows immune and inflammatory cells in AD. It is important to emphasize that the majority of T cells in AD skin lesions are cutaneous lymphocyte-associated antigen (CLA^+)$CD45RO^+$ memory T cells.[63,64] Due to recirculation, peripheral CLA^+T cells have similar features characteristic of T cells present in AD skin lesions.[65] Various skin T cells, such as CD4 TH1 cells, CD4 TH2, CD4 TH17, CD4 TH22, CD4 Treg, resident memory T cells, γδ T cells, CD8 TC1, CD8 TC2, Mucosal-associated invariant T cells (MAIT) are described in Table 3. One recent advancement in AD was evidence showing that circulating CLA^+ T cells can be a reliable peripheral biomarker of inflammatory events occurring in the skin.[65] There is conflicting literature regarding the diversity of T-cell receptor (TCR) repertoire in AD skin lesions and their relationship to nonlesional skin. In this context, Brunner *et al.* showed that nonlesional AD skin shares a TCR repertoire similar to lesional AD skin.[66]

Other cell types, such as innate lymphoid cells (ILC), mast cells, eosinophils, basophils, and inflammatory dendritic cell populations can be detected in AD skin.[67] In human skin mast cells, proteomic analysis identifies two novel mast cell proteins, L1CAM/CD171 and DPP4/CD26, that are potentially relevant to skin homeostasis.[68] Skin mast cell and sphingosine-1-phosphate (S1P) activation is a novel effector that initiates remodeling in AD.[69] Several ILC-modulating factors are dysregulated in AD and the levels of IL-25, IL-33, TSLP, and PGD2 are elevated in AD skin.[70] In addition, cell—cell interactions between ILC2s and keratinocytes lead to activation or suppression of ILC2s.[70] Identification of surface molecules on these cells involved in type 2 immunity could provide new therapeutic targets for the treatment of AD. Blom *et al.* identified, for the first time, the expression of CD200R by cells such as ILC2, Th2, and basophils. Interleukin-31 (IL-31), preferentially produced from Th2 cells, binds to the IL-31 receptor (IL-31R) expressed on sensory nerves. IL-31/IL31R signaling has recently been shown to play a critical role in the development of pruritus in AD.[71] In the skin, there exists at least three populations of antigen-presenting cells including Langerhans cells (LCs), monocyte-derived LC-like cells, and inflammatory dendritic epidermal cells (IDECs).[72] IDECs and LC-like cells have been found to be present in both steady states and inflammatory states, and they are present in AD.[73] LC and IDEC in AD skin do not respond to Toll-like receptor (TLR) 2 activation and may contribute to the inability to clear *S. aureus* infection.[74] LC in patients with AD carry the high-affinity receptor for IgE, FcεRI, and are engaged in the pathogenesis of AD. The aryl hydrocarbon receptor mediates the anti-inflammatory feedback mechanism in FcεRI-expressing human LC.[75]

Future therapeutic targets and experimental models for the treatment of atopic dermatitis

Although there are many available treatments for allergic diseases, AIT induces establishment of long-term clinical tolerance to allergens, resulting in the prevention of further development of allergic diseases and a role for primary prevention has also been suggested.[76] Among currently investigated AIT routes in FA, oral immunotherapy (OIT) involves the oral administration of increasing amounts of allergens.[76] The transcriptomic profiles of skin obtained from mice that were epicutaneously sensitized, but orally tolerized indicate that oral antigen administration provides protection against AD by the expression of genes regulating Th2 inflammatory responses and skin barrier function.[77,78] In a relevant mouse model of AD, another study reported the efficacy of topical ivermectin, a drug used for scabies and rosacea, improved AD by inhibiting the priming and activation of allergen-specific T cells.[79] Several recent studies have shown promising results in the use of mesenchymal stem cells for the treatment of AD.[80,81] Sah *et al.*

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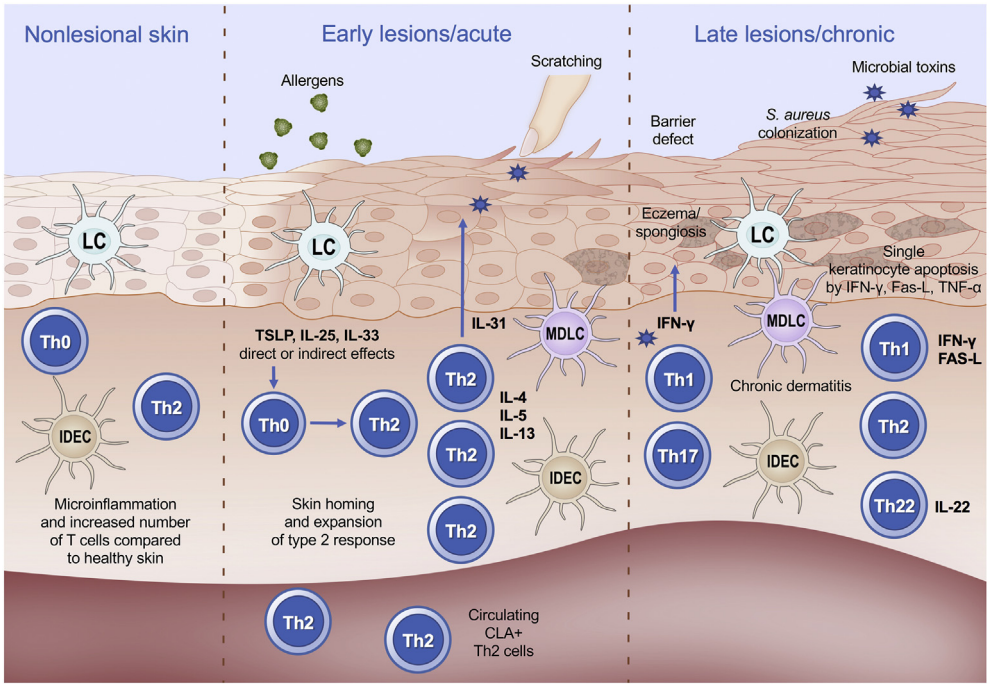

Fig. 1. T cells and dendritic cells in atopic dermatitis. T cells in uninvolved skin, early lesions and chronic lesions of type 2 AD. T cells are moderately increased in the dermis in the dermis of non-lesional skin. Skin homing CLA + T cells display a Th2 profile in early lesions and in the circulation. However, in the course of the disease, increasing populations of Th1 cells and IFN-γ and sometimes Th17 and Th22 cells are detected in chronic lesions of AD. IL-33, IL-25 and TSLP released from keratinocytes directly or indirectly support the type 2 response. IL31 released from T cells plays a major role in itch. Three populations of antigen-presenting cells including Langerhans cells (LCs) monocyte-derived LC-like cells, and inflammatory dendritic epidermal cells (IDECs) exist in the skin. IDECs and LC-like cells have been found to be present in both steady states and inflammatory states, and they are present in lesional AD.

Table 3
T cell subsets in the skin.

Different conventional and non-conventional T cells	Major functions
CD4 TH1	AD chronic lesions, ACD, drug exanthemas, mechanisms of eczema formation
CD4 TH2	AD lesions, AD and general allergy allergen-specific Th2, eosinophilic skin disease
CD4 TH17	AD chronic lesions, psoriasis, neutrophilic drug exanthemas
CD4 TH22	AD late lesions
CD4 Treg	Controls overactivation of other subsets in peripheral blood and lymphatic organs in AD, ACD. Does not exist too many in lesional skin
T_{RM}	Resident memory T cells, mainly against infectious agents, mostly CD8
γδ T cells	Against infectious agents in mice, very few in human skin
CD8 TC1	Against viruses and other infectious agents, found in AD and ACD skin and drug exanthemas
CD8 TC2	AD, eosinophilic skin diseases
MAIT cells	Mucosal-associated invariant T cells, against bacteria and fungi, riboflavin responsive and MR-1 tetramer responsive

AD, atopic dermatitis; ACD, allergic contact dermatitis.

explored the clinical potential for superoxide dismutase 3-transduced mesenchymal stem cells in mice with AD. They showed that subcutaneously administrated superoxide dismutase 3-transduced mesenchymal stem cells suppress skin inflammation via the histamine H4 receptor/IL-4 receptor-dependent mechanism.[81] Succinate is an intermediate of the citric acid cycle that binds to its specific receptor, SUCNR1/GPR91. In addition, it acts as an alarmin and is involved in tissue injury or inflammatory stimulus. Furthermore, GPR91, a metabolic control receptor for the binding of succinate, deficiency in mice leads to allergic contact dermatitis, suggesting that GPR91 is a therapeutic target for the treatment of allergic skin diseases.[82]

In humans, Kopfnagel *et al.* investigated the effect of RNAse 7, a 14.5-kDa antimicrobial ribonuclease on isolated human T cells.[83] They demonstrated that $CD4^+$ T cells from AD patients showed a less pronounced downregulation of IL-13 in response to RNAse 7 compared to healthy controls.[83] Thus, RNase 7 has immunoregulatory functions on Th2 cells and reduces the production of Th2 cytokines in the skin.

Many receptors have been studied, such as CCR4, CCR10, and CCR8, for the recruitment of immune cells to the skin.[84–86] Due to the complexity of AD, it would be interesting to target specific cells with cocktails of chemokine receptor antagonists administered as ointments on the skin.[84] In a randomized clinical trial of neonatal

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BCG vaccination in the Danish population, BCG vaccination at birth was found to be associated with less AD among children with atopic predisposition, although more studies are needed to confirm these findings.[87]

Precision medicine for food allergy: diagnosis and the role of biomarkers in early prediction

Molecular mechanism-linked therapies can be defined as therapies tailored to the characteristics of each patient to obtain a better clinical outcome. These different therapeutic responses linked to individual patient's biological mechanisms is known as precision medicine.[88] Precision medicine consists of four main components including disease taxonomy, digital monitoring of patients and biomarkers, disease phenotypes and endotypes, and biomarker- and endotype-linked patient care and therapies.[89] Three main pillars of precision medicine are endotypes, phenotypes, and biomarkers.[89] Important concepts such as regiotypes and theratypes have been recently introduced. Both regiotypes (regional differences in pheno and endotypes as well as allergens affecting different parts of the world) and theratypes (treatment response) represent important advancements for precision diagnosis and treatment.[6] Of all allergic diseases, FA is particularly well-suited as a target for precision medicine. This is due to its pathophysiology, the modulation of which has resulted in better clinical outcomes, and additionally has been clearly associated with detectable biomarkers[90,91] The consensus document of EAACI and American Academy of Allergy, Asthma and Immunology (AAAAI) has been recently published under the auspices of the PRACTALL collaboration platform.[92] PRACTALL is an initiative of EAACI and AAAAI to harmonize the European and American approach to allergic diseases with regard to patient treatment and scientific progress.[90] In the consensus document, special consideration was given to defining endotypes in order to assist in developing novel therapeutic approaches. The definition of endotypes in FA is necessary to develop novel therapeutic approaches. FA endotypes can be characterized into IgE-mediated endotypes, including alpha-gal allergy and oral allergy syndrome, and non-IgE-related and mixed endotypes such as food protein-induced gastrointestinal endotype and eosinophilic endotype.[93,94] Diagnostic tools and biomarkers for accurate diagnosis, evaluation of prognosis, and efficacy of treatment are still under investigation, but basophil activation test and component-resolved diagnostics are promising tools.[95,96] A recent systematic review showed that selected components of cow's milk, hen's egg, peanut, hazelnut, and shrimp allergen revealed high specificity for diagnosis of FA in component resolved diagnosis.[97,98] In a multicenter study, the detection of Ana o 3-specific IgE provides a predictive value in the diagnosis in children with suspected cashew allergy.[99] A combination of component-resolved diagnostics and other factors such as clinical background and extract-based serology has been proposed to predict severe reactions to hazelnut allergy.[100] Several biomarkers have been associated with FA including skin prick tests, allergen specific IgE, IgG4, genetic, and epigenetic markers.[92,101–104] A study of patients with meat allergy revealed that the IgG subclass distribution in these patients is distinct from natural IgG responses in nonallergic individuals.[105] Due to a frequent co-sensitization to birch pollen allergens and profilins, diagnosis of lipid transfer proteins (LTPs) using plant extracts is difficult.[106] In a study from a central European population, Pru p 3, peach LTP, can be used as an allergen marker for LTP sensitization.[107] To identify diagnostic markers for anaphylaxis in food allergic patients, Wittenberg *et al.* found serum levels of apolipoproteins as a useful biomarker of anaphylaxis.[108]

Early prediction of the severity of FA is one of the key issues for the accurate diagnosis and improved management. The extent to which the severity of food allergic reactions can be predicted by clinical factors such as age, type of food, and eliciting dose is currently unknown.[109] Several studies provided evidence that the eliciting dose contributes to the frequency of accidental reactions.[110,111] Another study suggests that individuals have a threshold of reactivity for symptoms in general as well as a threshold for symptoms specifically of anaphylaxis.[112] Additionally, a double-blind, placebo controlled study on patients with food challenge-confirmed FA to milk, egg, peanut, cashew, and/or hazelnut indicated that clinicians should not use the eliciting dose obtained from a graded food challenge.[109] This is because eliciting dose only contributes to reaction severity. A successful diagnostic allergy work-up is required to tailor medical treatments to individual characteristics of each FA patient.[113] Extensive immune and allergy workups are becoming more and more important for many diseases.[114] For FA diagnosis, a comprehensive toolbox for improved documentation and decision-making using oral food challenges has been provided.[115] With these tools, we hope to reduce the influence of subjective judgment of supervising physicians.[115]

Innovative solutions: allergen exposure chambers

Allergen exposure chambers have proven to be valuable tools for diagnosis and determining safety and efficacy of new therapeutics.[116–119] This tool can help to develop further evidence for allergen immunotherapy as well as biological therapies, which can potentially control allergic diseases.[120–122] Allergen exposure chambers also provide a new setting which has generated evidence that in patients with AD with grass pollen sensitization is linked to a worsening of cutaneous symptoms.[123] Although facilities have been reported as technically validated, various technical setups and specifications are found in allergen exposure chamber facilities.[124] Furthermore, several unmet needs require attention and evaluation before allergen exposure chambers can be used in allergen immunotherapy clinical trials.[125] Thus, it is necessary to standardize allergen exposure chambers, and harmonize protocols for clinical and immunological research in order to improve data quality and facilitate better application of allergen exposure chambers. Currently, the EAACI position paper harmonizes current concepts of allergen exposure chambers with regard to standardization of the challenge procedure and assessments, pediatric issues, and regulatory issues.[126] These relevant unmet needs and issues may be addressed before determining safety and efficacy of new therapeutics.[126]

Animal models in AD and FA

Animal models of human diseases are commonly utilized for the development of new drugs and the analysis of pathogenic research. Current animal research targets specific immune mechanisms involved in human atopic and allergic diseases.[127] In AD, AIT has been recently reported in a randomized controlled trial and meta-analysis, especially in patients sensitized to the house dust mite antigen.[128–130] However, there is still controversy about the role of AIT as a therapeutic intervention in AD. Several reasons exist for this, such as there is no relevant mouse model to investigate the mechanism and validate AIT in AD and primary end points were not achieved in several proof of concept clinical trials in AD. Shin *et al.* established an AIT model of AD using *Dermatophagoides farinae* treated NC/Nga mice and demonstrated clinical and histological improvement.[131] They found that induction of Tregs and IL-10-producing NK cells is a possible source of IL-10 and this model may be a useful tool to analyze the efficacy of AIT modalities for the treatment of AD.[131]

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In a recent study a method to directly assess *in vivo* the epidermal barrier function by electrical impedance (EI) spectroscopy was first time demonstrated in mice demonstrating a reliable diagnostic tool to detect skin barrier defects.[132] Mice epidermal barrier was damaged by epicutaneous application of proteases and cholera toxin and by tape stripping. EI and transepidermal water loss (TEWL) were measured before and after the application. A few hours after papain application, a dose-dependent reduction of EI was detected, reflecting the decreased barrier function. 24 and 48 h after the treatment, EI starts to increase to background levels, indicating tissue healing and restoration of skin barrier.[132] Barrier disruption was confirmed by histological analysis showing an impaired stratum corneum and higher cellular infiltration after papain application.[132] In addition, immunofluorescence staining and RT-PCR showed downregulation of molecules involved in the barrier function, such as filaggrin, occludin and claudin-1 and mRNA levels of filaggrin, loricrin, and involucrin. Comparable results were observed after tape stripping and cholera toxin treatment.

In FA, various animals have been used for studying the mechanisms of FA.[133] Adverse reactions to food also occur in companion animals and comparison between humans and animal models may lead to improved recommendations for the prevention and treatment of FA.[134] Similar to humans, companion animals may spontaneously develop skin, respiratory, and gastrointestinal tract symptoms.[135] However, there is no clear evidence between adverse food reactions and respiratory symptoms in companion animals.[136] For example, in dogs, adverse food reactions may manifest as cutaneous symptoms, which frequently are indistinguishable from AD due to environmental allergens.[137] In addition, little is known about the mechanisms of FA reactions in companion animals. In dogs, an allergen specific IgE response and $CD8^+$ T cell phenotype have been studied for the mechanism of FA.[138] Based on the current knowledge and the EAACI position paper, comparative studies of companion animals and humans suffering from FA may serve to fill knowledge gaps in this area.[136]

Mechanisms and pathophysiology of food allergy

In food allergic patients, exposure to food antigens elicits a type 1 hypersensitivity reaction, which induces anaphylaxis. Atopic diseases are significantly associated with food induced anaphylaxis both in children and adults, but not with anaphylaxis induced by drug and venom.[139] Oral tolerance is the mechanism by which we maintain a normal physiological response to food antigens, and the breakdown of oral tolerance is likely to be linked to sensitization to food allergens. In humans, early skin barrier disruption due to inflammation is associated with an increased risk of FA.[140,141] Environmental exposure to food allergens can occur in house and bed dust after hen's egg consumption.[142] Importantly, oral exposure is also one of the routs for sensitization to allergens.[143] Recently, Lexmond *et al.* demonstrated that a loss of function mutation in the Wiskott-Aldrich syndrome (Was) protein lead to an increased risk of FA.[144] They showed that $Was^{-/-}$ mice became sensitized to OVA upon oral administration in the absence of adjuvant, resulting in the development of IgE-mediated mast cell responses and FA. Studies from $Was^{-/-}$ mice will provide new insights into the pathophysiology of FA in humans. Vitamin D plays a critical role in the stabilization of mast cells, which automatically activate in vitamin D deficient conditions.[145] However, there is no evidence that vitamin D insufficiency during the first 6 month of infancy is a risk factor for IgE-mediated FA at 1 year of age.[146] Other factors such as genes (e.g., filaggrin gene mutation) and microbiome are also related to FA.[147] One potentially important gene is the signal transducer and activator of transcription 6 (STAT6), which stimulates Th2 differentiation. In this context, van Ginkel *et al.* identified for the first time that risk variants increase STAT6 expression and STAT6 variants may be involved in the pathogenesis of FA.[148] Multiple studies have provided evidence that FA is determined in part, by the microbiome.[141] Prior studies investigated the association in infants of the intestinal microbiome and allergic disease in humans.[37] In a prospective microbiome-wide association study, bacterial genera present in the infant intestinal microbiome were inversely associated with the development of food sensitization at the age of 3 years.[149] Recently, epigenetic mechanisms have been suggested to play a role in FA.[147,150] For example, differences in epigenetic changes in DNA methylation of the promoter region of Th1 and Th2 cytokine genes and Treg play a role in children with IgE-mediated cow's milk allergy.[151,152] Identification of specific miRNAs and their targets may help to understand the mechanism of FA. miR193a-5p is the most downregulated miRNA in children with cow's milk allergy and the inhibition of miR193a-5 resulted in elevation of protein level of IL-4.[153]

Although allergy to cow's milk and hen egg is more common among younger children, the mechanisms of the natural development of tolerance remains poorly understood.[154] They are typically sensitized with cow's milk proteins, such as casein and lactoglobulin.[155] IgG4 antibodies have been proposed to be a good indicator of the clinical efficacy of allergy treatments.[156] Recent analysis of IgG4 epitope binding in patients with cow's milk allergy in children revealed that the number of peptides bound by IgG4 antibodies and intensity of binding decreased when patients became tolerant, suggesting that these antibodies are important in tolerance acquisition.[157] Cow's milk formulas differ with regard to the degree of hydrolysis of the mild protein. In this context, several mild hydrolyzed cow's formulas are available and useful for the avoidance of cow's milk allergy in children due to different properties with regard to allergenic activity, IgE reactivity, T-cell proliferation, and cytokine secretion.[158] Tolerance to baked egg and cow's milk is related to conformational changes induced by heating.[159] However, reaction threshold data from 352 children, who underwent food challenges to fresh or extensively heated hen's egg and cow's milk found no significant shift in dose-distribution curves by baking process.[160]

Almost 70% of patients with birch pollen sensitivity have IgE-mediated reactions to plant foods such as hazelnut, apple, stone fruits, kiwi, and carrot, which typically cause oral allergy syndrome.[161,162] These food allergies are caused by a sensitization to Bet v 1 and subsequent IgE and T-cell cross-reactivity to food allergens.[161] Dau c 1 has been suggested as a major allergy in carrot allergic patients.[163] Dau c 1-specific T cell lines established from patients with birch pollen and carrot allergy indicated that T cell response to Dau c1 occurs independently of Bet v 1, suggesting that in addition to cross-reactivity with the major pollen allergens, Dau c 1 itself shows sensitization activity.[164]

Novel strategies for the treatment and management of food allergy

The current treatment approach of FA is strict avoidance of the offending food or foods and the use of rescue medication in the event of an allergic reaction.[165] Therefore, a significant amount of research has been conducted on food AIT including OIT, sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). The aim of food AIT is to achieve clinical desensitization, sustained unresponsiveness, and oral tolerance, which are essential for emerging therapies for FA.[166] The EAACI Task Force on Allergen Immunotherapy for IgE-mediated FA provided evidence-based recommendations for active treatment with AIT.[167] Food AIT has shown the greatest promise for children 4–5 years of age with

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symptoms suggestive of persistent IgE-mediated FA to cow's milk, hen's egg, or peanut.[167] In addition to the improvement of symptoms, quality of life of patients with FA improves during OIT for allergy.[168] In other words, a greater understanding of psychological and physical outcomes contribute to prevention and intervention in FA.[169] Current studies have enrolled patients with heterogeneous clinical symptoms.[170] Most children with milk and egg allergy develop tolerance spontaneously. Although OIT has been shown to be more efficient than SLIT, OIT has demonstrated a higher frequency of adverse events.[167] In clinical settings, increasing doses during the build-up phase should be performed in food AIT.[171] Novel studies have been conducted adding anti-IgE as a biological to improve food AIT. Addition of anti-IgE therapy reduces the allergic side effects of food AIT as it was shown for other AITs.[172,173] To ensure efficacy and safety of food AIT, patient factors such as age, co-existence of other allergic diseases, and adherence should be considered.[167,170] Development of education and training of primary care professionals, diagnosis and stratification of patients, and monitoring of treatment effectiveness are required for AIT.[174]

New developments in technology and the combination of two therapeutic strategies offers opportunities to improve treatment with AIT.[175] Encapsulation of allergens or DNA vaccines into nanoparticles may provide advantages compared to conventional AIT.[176,177] Srivastava *et al.*, investigated the efficacy and safety of peanut OIT using CpG-coated nanoparticles containing a peanut extract in a mouse model of peanut allergy.[178] They found that mice treated with the nanoparticles were significantly protected from anaphylaxis.[178] For the improvement of SLIT treatment, combination therapy with systemic administration of IL-2/anti-IL-2 complexes suppresses experimental FA in mice. Combination therapy may represent a promising strategy for the treatment and management of FA.[179] Another recent focus has turned to primary prevention of FA.[180] Early peanut introduction is one way to prevention, but early peanut recommendations differ among countries with formal guidelines.[181] Furthermore, there is evidence supporting that early egg introduction can decrease the risk of developing egg allergy.[182]

Conclusion

In conclusion, we have reviewed the recent developments on AD and FA. An important feature of these recent developments is that the era of precision medicine brings novel strategies in the management and treatment of AD and FA. Development of a prevention strategy, early interventions and psychological disturbance are important aspects of patient care. The emergence of novel diagnostic tools, innovative solutions, and biomarkers as well as novel mechanisms of AD and FA can be used to accelerate the development of novel drugs and targeted therapies. Identifying treatment effects and looking at candidate biomarkers in both animal models and humans will provide evidence to promote the ability to practice personalized treatment.

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Conflict of interest

CAA reports employment/leadership/advisory role in Regeneron, Sanofi Aventis, and Scibase. He has received research funding from Allergopharma, Novartis, Idorsia, Scibase, EU Horizon 2020 Cure, Swiss National Science Foundation, and Actelion. KS has no conflict of interest.

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